Contains Nonbinding Recommendations

Draft Guidance on Omega-3-Acid Ethyl Esters

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Omega-3-Acid Ethyl Esters

Form/Route: Capsule / Oral

Recommended studies: 1 In Vitro Study or 2 In Vivo Studies

In Vitro Option

Providing the recommendations on active pharmaceutical ingredient (API) in Appendix 1 and the recommendations on antioxidant in Appendix 2 are both met, the capsule fills of the Test and Reference drug products are considered very similar, and BE may be established based solely on an in vitro method (Quantitative Capsule Rupture Test described below) that assures equivalent release of API from the capsules.

Quantitative Capsule Rupture Test

A quantitative capsule rupture test method should measure the release of eicosapentaenoic acid ethyl ester (EPAee) and docosahexaenoic acid ethyl ester (DHAee) in an aqueous testing medium. In order to obtain an accurate release profile, the test samples should be taken at early times (e.g., 5, 10, 15, 20, 25 minutes) and as frequently as possible, until at least 80% of the drugs are released from the capsules. The method should demonstrate sufficient discrimination for detection of potential differences between formulations, with acceptable variability.

Based on the information available to the Agency, as well as the recommendation given in the USP Pharm Forum[1], USP Apparatus 4 (flow-through cell) has been shown to be the most appropriate apparatus for drugs with poor solubility, compared with the conventional USP Apparatus 1 (basket) and Apparatus 2 (paddle). In addition, the use of surfactant is also critical in the *in vitro* drug release method development for an Omega-3-Acid Ethyl Esters Capsule drug product.

The firm should develop the *in vitro* drug release method for the drug product using USP Apparatus 4 (flow-through cell). A second method using USP Apparatus 2 (paddle) may be developed in conjunction with the method using USP Apparatus 4 for comparison, if desired. The data from USP Apparatus 4, and from USP Apparatus 2 (if conducted), should be submitted to the Division of Bioequivalence for evaluation and for determination of the most suitable method.

The firm should provide all dissolution method development data showing that the dissolution

[1] Marques MRC, Cole E et al., Stimuli to the Revision Process: Liquid-filled Gelatin Capsules. *USP Pharm Forum 2009;35(4, July-Aug)1029-41.*

method(s) studied have been systematically optimized for (but not limited to) the following parameters:

1. Dissolution medium and volume
2. Surfactant and concentration
3. Filter type and size for sample collection and preparation, where applicable
4. Enzyme and concentration, where applicable
5. Rotation speed (USP Apparatus 2 (paddle))
6. Flow rate (USP Apparatus 4 (flow-through cell)

Other parameters for USP Apparatus 4:

7. System mode (closed versus open)
8. Type of cell (size in mm)
9. Glass beads (size in mm)
10. Glass bead loading (weight in gm)
11. Sample load (volume in mL)
12. Split ratio (%)
13. Size of sample tube (volume in mL)

For each parameter, at least 5 values, in addition to zero value, around the selected final value should be tested in the optimization. The optimization data should demonstrate that the selected value is optimal and appropriate. For example, in order to select the final drug release medium of 0.5% Sodium Lauryl Sulfate (SLS), data from testing using the media of 0%, 0.25%, 0.35%, 0.65% and 0.75% SLS should also be submitted for comparison. In addition, other scientific justifications and evidence may be submitted to support the choices of the final parameter values. Optimizing testing should employ 6 dosage units for each determination. For final testing using the optimized method, 12 dosage units each of the test and reference products should be employed.

NOTE: It is critical that for USP Apparatus 4, when used for lipid-filled soft gelatin capsule (SGC) dosage forms, a modified flow-through cell designed for SGC[2] be used in the testing. For USP Apparatus 2, when used for this dosage form, the sampling probes should remain immersed in the dissolution medium throughout the duration of testing in order to obtain reproducible results. The use of a sinker with USP Apparatus 2 may be considered in preventing the capsules from floating to the top.

In Vivo Option

Providing equivalence of API is established by meeting the qualitative and/or quantitative criteria specified in Appendix 1, BE may be established by conducting in vivo studies with pharmacokinetic endpoints. Two in vivo BE studies are recommended.

1. Type of study: Fasting
   Design: Single-dose, partial or fully replicated crossover *in-vivo*

[2] USP *Revision Bulletin* Official August 1, 2011 <2040> Disintegration and Dissolution of Dietary Supplements.

Strength: 1 gram contains at least 900mg of the ethyl esters of Omega-3 fatty acids (Dose: 4×1 gram capsules)
Subjects: Healthy males and nonpregnant females, general population.
Additional Comments: (1) In using the reference-scaled average bioequivalence approach for Omega-3-Acid Ethyl Esters capsules, please provide evidence of high variability in the bioequivalence parameters of AUC and/or Cmax (i.e., within-subject variability ≥ 30%). For details on the method for statistical analysis using the reference-scaled average bioequivalence approach, please refer to the draft Progesterone Oral Capsule Guidance at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM209294.pdf. (2) We recommend that the applicant control the subjects' diet from at least 48 hr prior to till at least 36 hr after drug administration. We recommend EPA and DHA limited meals throughout the diet control period. (3) We recommend that baseline measures be calculated from an average of three or more (>3) samples collected between 24 and 0 hours (inclusive) prior to dosing.

Analytes to measure (in appropriate biological fluid):

(1) EPA total lipids in plasma
(2) Baseline-adjusted EPA total lipids in plasma
(3) DHA total lipids in plasma
(4) Baseline-adjusted DHA total lipids in plasma
(5) EPA free fatty acids in plasma
(6) Baseline-adjusted EPA free fatty acids in plasma
(7) DHA free fatty acids in plasma
(8) Baseline-adjusted DHA free fatty acids in plasma

Bioequivalence based on (90% CI):

(1) Baseline-adjusted EPA total lipids
(2) Baseline-adjusted DHA total lipids

Please submit the data of baseline-adjusted EPA and DHA free fatty acids and the statistical analysis using the reference-scaled average bioequivalence approach as supportive evidence.

2. Type of study: Fed
Design: Single-dose, partial or fully replicated crossover *in-vivo*
Strength: 1 gram contains at least 900mg of the ethyl esters of Omega-3 fatty acids (Dose: 4×1 gram capsules)
Subjects: Healthy males and nonpregnant females, general population.
Additional Comments: We recommend a high-fat, high-calorie, EPA and DHA-limited test meal for fed BE study. Please also see comments in the study above.

Analytes to measure (in appropriate biological fluid):

(1) EPA ethyl esters in plasma
(2) DHA ethyl esters in plasma

(3) EPA total lipids in plasma
(4) Baseline-adjusted EPA total lipids in plasma
(5) DHA total lipids in plasma
(6) Baseline-adjusted DHA total lipids in plasma
(7) EPA free fatty acids in plasma
(8) Baseline-adjusted EPA free fatty acids in plasma
(9) DHA free fatty acids in plasma
(10) Baseline-adjusted DHA free fatty acids in plasma

Bioequivalence based on (90% CI):

(1) EPA ethyl esters
(2) DHA ethyl esters

Please submit the data of baseline-adjusted EPA and DHA total lipids and baseline-adjusted EPA and DHA free fatty acids, and the statistical analysis using the reference-scaled bioequivalence approach as supportive evidence.

Dissolution Test Method and Sampling Times:

Please note that a **Dissolution Methods Database** is available to the public at the OGD website at http://www.accessdata.fda.gov/scripts/cder/dissolution/ . Please find the dissolution information for this product at this website. Please conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products.

APPENDIX 1
API EQUIVALENCE

Omega-3-Acid Ethyl Esters is a natural source drug obtained from the body oil of several fish sources. The Omega-3-Acid Ethyl Esters USP monograph defines the active pharmaceutical ingredient (API) as composed of seven individual omega-3-acid ethyl ester components. The Omega-3-Acid Ethyl Esters Capsules USP monograph[3] establishes ranges for the two most abundant components (EPAee and DHAee) of the active pharmaceutical ingredient (API) and ranges for the sum of the two components. The reference product contains lesser quantities of the other five omega-3 acid ethyl esters, although quantitative ranges are not specified in the USP monographs. The Agency has determined the quantitative ranges of the other five omega-3-acid ethyl ester components based on assay of multiple batches of the RLD using the USP monograph analytical method.

The agency's recommendation for each component of the API varies with its content. API in each batch of a Test product must meet the quantitative ranges for all the seven components. The following are the specifications for each individual component of API. The unit of mg/g in the current recommendation means mg per gram of encapsulated oil.

1. Most abundant components: EPAee and DHAee

Eicosapentaenoic acid ethyl ester (EPAee; C20:5 n-3)	430 - 495 mg/g
Docosahexaenoic acid ethyl ester (DHAee; C22:6 n-3)	347 - 403 mg/g
Sum of EPAee and DHAee	800 - 880 mg/g
Total omega-3 acid ethyl esters	NLT 90% (w/w)

2. Additional components present at greater than or equal to 10 mg/g encapsulated oil: SDAee, HPAee, DPAee

Moroctic acid ethyl ester (SDAee; C18:4 n-3)	4.0-37.0 mg/g
Heneicosapentaenoic acid ethyl ester (HPAee; C21:5 n-3)	7.9-31.4 mg/g
Docosapentaenoic (Clupanodonic) acid ethyl ester (DPAee; C22:5 n-3)	16.3-50.0 mg/g

3. The component present within the range of ≥1 - <10 mg/g encapsulated oil: ETAee

Eicosatetraenoic acid ethyl ester (ETAee; C20:4 n-3)	Present

4. The component present at below 1 mg/g encapsulated oil: ALAee

The content of Alpha-linolenic acid ethyl ester (ALAee; C18:3 n-3) is below 1 mg/g in the reference product, and it will not be considered in the pharmaceutical equivalence assessment.

[3] Omega-3-Acid Ethyl Esters Capsules monograph, USP-35, official from August 1, 2012

APPENDIX 2
INACTIVE INGREDIENTS

1. Alpha-tocopherol

The formulation of the RLD encapsulated oil contains a labeled concentration of antioxidant:[4]

Alpha-tocopherol	4 mg/g encapsulated oil

Alpha-tocopherol should be present in the same concentration as in the RLD. The alpha-tocopherol may be either the natural d-alpha-tocopherol, or the synthetic dl-alpha-tocopherol.

2. Soybean oil

The test product may either contain or not contain soybean oil, depending on the commercial source of alpha-tocopherol. We recommend that a test product not add soybean oil unless it is present in the commercial form of alpha-tocopherol used by the ANDA applicant.

[4] LOVAZA Capsules labeling, revised 22 December 2010